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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,350	11/30/2001	Peter P. Roller	214683	5514

23460 7590 09/03/2004

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EXAMINER	
CHANDRA, GYAN	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,350	ROLLER ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *3,4,7,8 and 10-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group I, claims 1,2,5,6, and 9 in the reply filed on 06/21/04 is acknowledged. The traversal is on the ground(s) that Applicant argues that there is a slight burden but not serious search burden, since all of the claims require search of substitution of a cyclic peptide. This has been fully considered but is not found to be persuasive because the other claims do not necessarily require the cyclic peptide of claim 1, such as claims 3-4, 7-8, and 10-22. The requirement is still deemed proper and is therefore made FINAL.

Claims 3-4, 7-8, and 10-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse based on an incomplete response.

Applicants' election with traverse of Species of (a) sulfoxide as the "L" moiety and (b) a single peptide as the carrier of the conjugate is also acknowledged.

Priority

This application lacks the necessary reference to the prior provisional application. A statement reading " This application claims benefit of PCT Application US00/15201 filed on 06/ 02/ 2000 and Provisional Application No. 60/137187, filed on 06/02/1999."

should be entered following the title of the invention or as the first sentence of the specification.

Status of Application, Amendments, and/or Claims

Your response to " NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES" on 12/09/2002 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,2, 5,6, and 9 are rejected under 35 U.S.C. 112, first paragraph, because specification, while being enabling for the method of making the claimed cyclic compound, does not reasonably provide enablement for therapeutic administration of the compound *in vivo*.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of

sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a cyclic peptide of SEQ ID NO: 1. The claim reads that the cyclic peptide is non-phosphorylated and redox stable *in vivo*, and binds to an SH2 domain in a protein comprising an SH2 domain. The cyclic peptide has an IC_{50} less than 4.0 μM with the target protein growth factor receptor-bound protein 2 (Grb2). The in vivo IC50 data in specification contemplate administration of the peptide in specifically recited dose for treatment of cancer or specifically for breast cancer. Dependent claims recite a conjugate of the cyclic peptide with a signal peptide and a carrier for to facilitate its delivery.

The state of the prior art and the predictability or lack thereof in the art: The specification teaches how to synthesize a peptide with SEQ ID NO: 1 and provides guidance to one

skilled in the art to add "L" moiety as a Sulfoxide (SO) and a signal peptide as a carrier agent (examples 4 and 12). Applicants contemplate administering the cyclic peptide with SEQ ID NO: 1 to prevent breast cancer. However, the specification does not provide any detailed guidance to achieve this from an in vitro binding assay in an established cell line. Applicants' example of the cyclic peptide and its IC 50 from MDA-MB-453 cell line for its intended use is highly unpredictable of therapeutic efficacy *in vivo* due to vascular and interstitial barriers to delivery of the agents to the tumor site (see Jain, Cancer and Metastasis Reviews 9:253-266, 1990, the abstract, and Jain, Science 271:1079-1080, 1996, page 1080, first full paragraph). Monks et.al. (J. Natl. Cancer Inst. 83: 757-766, 1991) described the development and implementation of a pilot-scale, in vitro anticancer drug screen utilizing a panel of 60 cell lines. This was to improve the quality of screen and does not predict *in vivo* outcome. Dermer (Bio/Techonology, 12 : 320, 1994) reports that the reason cell lines have become the standard for determining what cancer should be like is because of their convenience for experimentation and the petri dish cancer is really a poor representation of malignancy, with characteristic profoundly different from the human disease. Landon et. al. (2003) report that it has been found that peptides selected in vitro or in situ may not effectively target tumors *in vivo* due to poor peptide stability and other problems. Lung et. al., (Biopolymers, 71:132-140, 2003) teach under the section " Modification the Permeability of Peptide Analog Toward Drug Delivery" on page139 that – In *in vivo* studies, the cell permeability of the large highly charged, peptide inhibitors to the breast cancer cell lines

might become a problem. Therefore, the teachings of the art are that efficacy of peptide therapeutics *in vivo* is highly unpredictable.

The amount of direction or guidance present and the presence or absence of working examples: Applicants have provided two examples (i) with MDA-MA-453 cell lysate and (ii) with pre-treatment of MDA-MB-453 cells with the peptide of SEQ ID NO: 1 in the instant specification. Given the general teachings in the art of the unpredictability of *in vivo* administration of peptide, as therapeutic enablement must be provided in the instant disclosure. The specification lacks any teachings on how one skilled in the art can use the cyclic peptide of SEQ ID NO: 1 as a therapeutic for administering in a subject with breast cancer or other diseases. The working examples describing assays for inhibition of growth factor receptor, MAP Kinase, and the interaction of between erbB-2 and Grb2 in the MDA-MB-453 cell line are limited to in vitro cell assays. The specification fails to provide guidance as to how to administer the peptide to a subject for successful treatment or breast cancer or any other disease.

The breadth of the claims and the quantity of experimentation needed: Given the teachings of unpredictability found in the art regarding the efficacy of cyclic peptides for inhibiting breast cancer and given the lack of sufficient teachings in applicants' disclosure to overcome the teachings of unpredictability found in the art, it would require undue experimentation by one skill in the art to be able to practice the claimed invention.

Conclusion

No claims are allowed.

Claims 1, 2, 5,6, and 9 are appear to be free of the prior art.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Landon et.al., J. Cell. Biochem. 90:509-517 (2003). The authors describe peptide selection with optimum in vivo properties using tumor-bearing animals.

2. Lung et.al., Biopolymers 71:132-140 (2003). The authors report difficulties of peptide inhibitors in *in vivo* studies.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571)272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

Gyan Chandra
AU 1646
19 August, 2004